

Appl. No. : 09/403,440  
Filed : January 19, 2000

Please replace the paragraph starting at page 7, line 9 with the following new paragraph:

-- Variant peptides have an amino acid sequence which differs from wt p53 sequence, e.g. in the motif between amino acids 13-41 described in WO 96/02642, by one or more of addition, substitution, deletion and insertion of one or more amino acids, but which retains the activity of binding to mdm2. Such variants preferably include the motif FXaaXaaXaaW (SEQ ID NO: 4), where Xaa is any amino acids, and will typically share at least about 70%, more preferably at least about 80%, more preferably at least about 90%, or more preferably at least about 95% amino acid sequence identity with the corresponding portion of human p53. Examples of peptides capable of disrupting the interaction of p53 and mdm2 are the thioredoxin insert peptides (TIPs) disclosed in Böttger et al, 1996, and in the examples below, see especially peptide TIP 12/1.

Please replace the paragraph starting at page 20, line 2 with the following new paragraph:

-- pTrx (Invitrogen) was cleaved with RsrII. The following oligomers were phosphorylated, annealed and then ligated into the cleaved vector:

For TIP wt: 5' - 3'

GTCCGCCTCTGAGTCAGGAAACATTTTCAGACCTATGGAACTACTTCCTGAAAACG  
(SEQ ID NO: 5)

and 5' - 3'

GACCGTTTTTCAGGAAGTAGTTTCCATAGGTCTGAAAATGTTTCCTGACTCAGAGGCG  
(SEQ ID NO: 6)

For TIP 12/1: 5' - 3'

GTCCGCCTCTGAGTATGCCTCGTTTTATGGATTATTGGGAGGGTCTTAATGAAAACG  
(SEQ ID NO: 7)

and 5' - 3'

GACCGTTTTTCATTAAGACCCTCCCAATAATCCATAAAACGAGGCATACTCTCAGAGG  
CG (SEQ ID NO: 8).

Please replace the sentence at page 20, lines 15-16 with the following new sentence:

-- The resulting peptide inserts are illustrated in Figure 1 (SEQ ID NOS: 2 and 3).

Please replace the paragraph starting at page 21, line 5 with the following new paragraph:

-- For cloning of TIP 12/1, TIP wt and Trx into pcDNA3 for expression in mammalian cells, the thioredoxin coding region complete with the peptide insertions, was amplified from pTrx, pTrx 12/1 and pTrx wt using the following primers:

5' - 3': CGGGATCCACCATGGGCGATAAAATTATTACCTG (SEQ ID NO: 9) and  
5' - 3' CTCGACGCTAACCTGGCCTAGGGAATTCC (SEQ ID NO: 10).

Please replace the paragraph starting at page 24, line 16 with the following new paragraph:

-- Construction of  $F^{19} \rightarrow A$  was accomplished by site directed mutagenesis using the Transformer<sup>TM</sup> site directed mutagenesis kit (Clontech). The sequence of the selection primer was: 5' - 3' GACTCTGGGGATCGATATGACCGACC (SEQ ID NO: 11), the sequence of the mutagenis primer was: 5' - 3' GAGCCAGGAGACAGCCTCAGGCTTATG (SEQ ID NO: 12). The sequence of the p53 mutant  $F^{19} \rightarrow A$  was confirmed by sequencing.

In the Claims:

Please amend claim 5 to read as follows:

5. (Twice amended) The method of claim 3 wherein the agent includes the peptide motif FXaaXaaXaaW (SEQ ID NO: 4), where Xaa is any amino acid.

Please amend claim 16 to read as follows:

16. (Twice amended) The method of claim 12 wherein the agent includes the peptide motif FXaaXaaXaaW (SEQ ID NO: 4), where Xaa is any amino acid.